REMARKS

Claims 1-3, 5-18, 20-22, 32, 34 and 35 were pending in this application. Claim 21 is now cancelled without prejudice to Applicants' right to prosecute its subject matter in the present application and in related applications. Claims 1, 7, 9, 18, 20 and 32 are currently amended without any intent of disclaiming equivalents thereof. Accordingly, upon entry of this paper, claims 1-3, 5-18, 20, 22, 32, 34 and 35 are pending and presented for consideration.

Claim amendments

Independent claim 1 is amended to clarify that the second complex comprises the first particle, the second member, the first member, the third member and the second particle. Support for the amendment can be found in the specification at least, for example, in paragraph 0012, and in Figure 1.

Independent claim 18 is amended to specifically recite "wherein the second member and the third member do not bind to each other." Support for the amendment can be found in the specification at least, for example, in paragraph 0042.

In addition, claims 1, 7, 9, 18, 20 and 32 are amended for clarification and consistency.

Applicants submit the amendments to the claims introduce no new matter.

Information disclosure statement

The undersigned wishes to thank the Examiner for forwarding to the Applicants a copy of the initialed, signed and dated PTO-1449 form originally submitted to the USPTO on April 15, 2005. However, Applicants respectfully request that the Examiner also consider the art cited in the PTO-1449 form originally submitted to the USPTO on February 15, 2002, and confirm this by initialing, signing and dating the PTO-1449 form. Applicants respectfully request that the Examiner return a copy of the initialed, signed and dated PTO-1449 form to the undersigned for completion of Applicants' files.

In addition, Applicants submit together with this response a fourth supplemental Information Disclosure Statement and accompanying Form PTO-1449 listing publications in accordance with the provisions of 37 C.F.R. §§ 1.97 and 1.98 for consideration by the Examiner in connection with the examination of the present patent application.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 9 and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that the recitation of C4BP protein or a fragment thereof in claims 9 and 18 is vague because it is unclear as to what this structure entails. *See*, the Office Action, page 2.

Without acquiescing to the rejection, and solely to advance prosecution, Applicants have amended claims 9 and 18 to further clarify that the second member comprises "C4BP or a fragment of C4BP that binds to protein S." [Emphasis added.] Applicants submit that the scope of the amended claims 9 and 18 is clear and definite because the protein S binding site on C4BP is well known in the art at the time of filing of the present application. Applicants submit as evidence a scientific paper by Hardig Y., *et al.* published in 1996, prior to the priority date of the present application, reporting that the entire protein S-binding site on C4BP is located within β-chain N-terminal short consensus repeat 1 (SCR-1). *See*, Hardig Y., *et al.* (1996) "The amino-terminal Module of the C4b-binding Protein β-chain Contains the Protein S-binding Site," J. Biol. Chem., 271:20861-20867, a copy of which is enclosed as Exhibit A. Therefore, Applicants submit that one skilled in the art would readily understand what structure is required for a fragment of C4BP that binds to protein S. Therefore, Applicants submit that the scope of claims 9 and 18 is clear and unambiguous. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 9 and 18 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the scope of the claims is allegedly not commensurate with the scope of the enabling disclosure. Specifically, the Office Action alleges that the specification, while being enabling for the C4BP protein, does not reasonably provide enablement for a fragment of the protein, because, according to the Office Action, it would require undue experimentation to predict which part of the fragment would retain its affinity without structural information. *See*, the Office Action, page 3. Applicants traverse the rejection to the extent it is maintained over claims 9 and 18 as amended.

The test for enablement is whether one reasonably skilled in the art could make or use the invention as broadly as it is claimed based on the disclosures in the specification coupled with information known in the art without undue experimentation. *See In re* Wands, 858 F.2d 731 (CAFC 1988). In Wands, the court faced the question whether the specification of the Wands patent enabled one skilled in the art to make high affinity IgM monoclonal antibodies for hepatitis B-surface antigen. The Wands court recognized that the nature of monoclonal antibody technology involved screening hybridomas to determine which ones secrete antibodies with desired characteristics. Id. at 740. The court stated: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue,' not 'experimentation.'" Id. at 736-737. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 737. In deciding whether undue experimentation is involved for practicing the invention as claimed, the court considered the following eight factors: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the

breadth of the claims." Id. at 737. The court concluded that undue experimentation would not be required to practice the invention because (1) Wands' disclosure provided considerable direction and guidance on how to practice the invention, (2) there was a high level of skill in the art at the time when the application was filed, and (3) all of the methods needed to practice the invention were well known. Id. at 737, 740.

Applying the Wands analysis to the present application, Applicants submit that one of ordinary skill in the art would readily be able to make or use the invention as claimed in claims 9 and 18 based on the disclosures in the specification coupled with information known in the art without undue experimentation. Claims 9 and 18, as amended, specifically recite that the second member comprises "C4BP or a fragment of C4BP that binds to protein S." [Emphasis added.] The Office Action alleges that it would require undue experimentation to predict which part of the fragment would retain its affinity without structural information. Applicants respectfully disagree. As discussed above, the structural information with respect to the protein S binding site on C4BP is well known in the art at the time of filing of the present application. Applicants have submitted as Exhibit A a scientific paper by Hardig Y., *et al.* published in 1996, prior to the priority date of the present application, reporting that the entire protein S-binding site on C4BP is located within β-chain N-terminal SCR-1. *See*, Exhibit A. Therefore, contrary to the Office Action's allegation, Applicants submit that one of ordinary skill in the art would readily be able to predict what fragment of C4BP would retain its binding affinity to protein S based on the structural information regarding the protein S binding site on C4BP available in the art when the present application was filed.

Applicants further submit that it was well within routine skills of an ordinary artisan at the time of filing of the present application to make and use a fragment of C4BP that binds to protein S. As the Office Action acknowledged, there is a high level of skill in the relevant art. Applicants submit that all of the methods needed to practice the invention were known in the art. For example, the Office Action acknowledged that it is within the skill of an artisan to make fragments of proteins (*see*, the Office Action, page 3). For example, methods for making various

fragments of C4BP were disclosed on pages 20862 and 20863 of Exhibit A. Applicants further submit that methods needed to test whether a particular fragment of C4BP binds to protein S were well known in the art when the application was filed. For example, assays to test the binding between protein S and various fragments of C4BP were described on page 20864 of Exhibit A. Additional binding assays, for example, yeast two-hybrid assays, phage display assays, were well known in the art when the present application was filed.

Therefore, Applicants submit that undue experimentation would not be required to practice the invention as claimed in claims 9 and 18 because (1) the structural information with respect to the protein S binding site on C4BP was available in the art at the time when the application was filed, and (2) all of the methods needed to practice the invention were well known in the art. Accordingly, Applicants respectfully request the rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-3, 7, 10 and 11 stand rejected under 35 U.S.C. §102(b) as being anticipated by Cambiaso (U.S. Patent No. 4,184,849). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

For a rejection to be proper under 35 U.S.C. §102, each and every element of the claimed invention must be identically disclosed or described in a single prior art reference. *In re Bond*, 910 F.2d 831, 832, 15 U.S.P.Q.2d (BNA) 1566, 1567 (Fed. Cir. 1990) (quoting *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677, 7 U.S.P.Q.2d (BNA) 1315, 1317 (Fed. Cir. 1988). Emphasis added.

Claim 1, as amended, recites a method to detect an unbound form of a first member of a binding pair by, *inter alia*, "forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle, wherein the third member bound to the second particle binds to the first member in the first complex" and "detecting the formation of the second complex by measuring an increase of the turbidity of the sample thereby

detecting the unbound form of the first member in the sample." Applicants submit that Cambiaso does not teach or suggest such a method. Cambiaso teaches a mixed agglutination assay to detect the presence of antibodies (Abs) or antigens (Ags) in a liquid by mixing the liquid with first and second particulate reagents which mutually agglutinate but whose agglutination is inhibited by the particular antibody or antigen in the liquid under assay. *See, e.g.*, Cambiaso, abstract, columns 1 and 2. Specifically, as set forth on column 2, lines 21-27, Cambiaso states: "Binding of the particulate reagent with the free Ab or Ag under assay blocks the binding sites on the particulate reagent so that it is no longer able to bind and agglutinate with the other particulate reagent. The extent of agglutination in the mixture is thus reduced (over that amount which would occur in the absence of the particular Ag or Ab from the liquid) by an amount dependent on the amount of the particular Ag or Ab under assay in the liquid. By observing this phenomenon, the presence of the particular Ab or Ag can be confirmed, and by measuring the extent of agglutination or non-agglutination, the amount of the particular Ab or Ag can be determined." [Emphasis added.] Thus, Cambiaso teaches a method that requires the first and second particulate reagents and the unbound Ab or Ag in the liquid compete for binding. In other words, in Cambiaso's method, the unbound Ab or Ag (which corresponds to the first member) can not simultaneously bind to the first particulate reagent (which corresponds to the first particle bound to the second member) and the second particulate reagent (which corresponds to the second particle bound to the third member), which is exactly the opposite of what's claimed in Applicants' claim 1. Therefore, Cambiaso clearly does not teach or suggest a method that includes a step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as required by Applicants' claim 1. Applicants submit that Cambiaso fails to anticipate claim 1 and its dependent claims because Cambiaso does not teach or suggest at least one required element. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103(a) over Cambiaso in view of Koike

Claims 5, 6, 8, 9, 13, 18, 20-22, 32, 34 and 35 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cambiaso in view of Koike (US Patent No. 5,187,067). Without acquiescing to the rejection and solely to advance prosecution, Applicants have cancelled claim 21, thus rendering the rejection with respect to claim 21 moot. Applicants traverse the rejection to the extent it is maintained over the remaining claims as amended.

Claims 5, 6, 8, 9, 13 and 32

Even if, *arguendo*, the disclosures of Cambiaso and Koike were combined, such a combination would not teach Applicants' invention as claimed in independent claim 1. As discussed above, Cambiaso does not teach or suggest a method that includes a step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as required by independent claim 1. Koike does not correct the deficiency of Cambiaso. Koike merely discloses conventional ELISA methods for detecting protein S in a sample using antibodies specific against free protein S or the protein S/C4BP complex (*see, e.g.*, Koike, abstract, column 2, lines 24-48). Koike does not teach or suggest any method that includes a step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as required by independent claim 1. Therefore, Applicants submit that neither Cambiaso nor Koike teaches the required step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as recited in independent claim 1.

Furthermore, as discussed above, Cambiaso teaches a method that requires that the unbound Ab or Ag (which corresponds to the first member) can not simultaneously bind to the first particulate reagent (which corresponds to the first particle bound to the second member) and the second particulate reagent (which corresponds to the second particle bound to the third member). Thus, Cambiaso teaches away from forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as required by independent claim 1. Therefore, Applicants submit that it would not have been

obvious for one of ordinary skill in the art to combine the teachings of Cambiaso and Koike to produce the method as claimed in claim 1. Therefore, Applicants submit that claim 1 and its dependent claims including claims 5, 6, 8, 9, 13 and 32 satisfy the requirement of 35 U.S.C. § 103.

Claims 18, 20, 22, 34 and 35

Even if, *arguendo*, the disclosures of Cambiaso and Koike were combined, such a combination would not teach Applicants' invention as claimed in independent claim 18. Independent claim 18, as amended, relates to a composition or a kit for detecting free protein S in a sample comprising a first particle bound to a second member comprising C4BP or a fragment of C4BP that binds to protein S and a second particle bound to a third member, wherein the second member and the third member do not bind to each other. Neither Cambiaso nor Koike teaches or suggests such a composition or a kit. As discussed above, Cambiaso uses first and second particulate reagents that mutually agglutinate to detect the presence of antibodies or antigens in a liquid. Specifically, as set forth on column 1, lines 48-62, Cambiaso teaches that the first particulate reagent comprises a solid particulate support material carrying a first substance and the second particulate reagent comprises a solid particulate support material carrying a second substance and requires that the said first substance (which corresponds to the second member) is capable of binding with the said second substance (which corresponds to the third member) to cause the first and second reagents to agglutinate together. Therefore, Applicants submit that Cambiaso at least does not teach or suggest a first particle bound to a second member comprising C4BP or a fragment of C4BP that binds to protein S and a second particle bound to a third member, wherein the second member and the third member do not bind to each other, as required by claim 18.

Koike does not correct the deficiency of Cambiaso. Koike teaches certain components required for carrying out conventional ELISA methods. For example, Koike teaches monoclonal antibodies specific against free protein S or the protein S/C4BP complex that are fixed to insoluble carriers suitable for ELISA methods (*see, e.g.*, Koike, abstract, column 2, lines 24-48).

Koike is silent with respect to components suitable for agglutination assays. In particular, Koike does not teach or suggest a first particle bound to a second member comprising C4BP or a fragment of C4BP that binds to protein S and a second particle bound to a third member that does not bind to the second member, as required by claim 18.

Therefore, Applicants submit that it would not have been obvious for one of ordinary skill in the art to combine the teachings of Cambiaso and Koike to produce the composition or kit as claimed in claim 18. Therefore, Applicants submit that claim 18 and its dependent claims including claims 20, 22, 34 and 35 satisfy the requirement of 35 U.S.C. § 103.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5, 6, 8, 9, 13, 18, 20-22, 32, 34 and 35 under 35 U.S.C. § 103(a).

Rejections under 35 U.S.C. § 103(a) over Cambiaso in view of Mischak

Claims 12 and 14-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cambiaso in view of Mischak (US Patent No. 6,124,430). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Even if, *arguendo*, the disclosures of Cambiaso and Mischak were combined, such a combination would not teach Applicants' invention as claimed in independent claim 1. As discussed above, Cambiaso does not teach or suggest a method that includes a step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle as required by independent claim 1. Mischak does not correct the deficiency of Cambiaso. Mischak teaches a method for rapid and direct quantification of hBNP levels in biological fluids using specific antibodies against hBNP. Mischak is silent with respect to agglutination assays that include a step of forming a second complex comprising the first particle, the second member, the first member, the third member and the second particle. Therefore, Applicants submit that it would not have been obvious for one of ordinary skill in the art to combine the teachings of Cambiaso and Mischak to produce the method as claimed in claim 1. Therefore, Applicants submit that claim 1 and its dependent claims including claims 12

and 14-17 satisfy the requirement of 35 U.S.C. § 103 and respectfully request the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103(a) over Cambiaso in view of Koike and in further view of Zuk

Claims 18 and 20-22 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cambiaso in view of Koike and in further view of Zuk (U.S. Patent No. 4,281,061). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

As argued above, independent claim 18 and any claims dependent therefrom are novel and unobvious over Cambiaso in view of Koike. Zuk does not correct the deficiency of Cambiaso or Koike. Zuk teaches methods and compositions for enhancing the sensitivity of immunoassays. Zuk is silent with respect to components required for agglutination assays. In particular, Zuk does not teach or suggest a first particle bound to a second member comprising C4BP or a fragment of C4BP that binds to protein S and a second particle bound to a third member that does not bind to the second member as required by claim 18. Therefore, Applicants submit that it would not have been obvious for one of ordinary skill in the art to combine the teachings of Cambiaso, Koike and Zuk to produce the composition or kit as claimed in claim 18. Therefore, Applicants submit that claim 18 and its dependent claims including claims 20 and 22 satisfy the requirement of 35 U.S.C. § 103 and respectfully request the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 1-3, 5-18, 20, 22, 32, 34 and 35 are in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,

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